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(54) Penetration enhancement systems and the preparation thereof.

(57) The application describes a transmembranally administrable composition comprising:

- (a) about 0.2% to about 5% of bioaffecting agent,
- (b) about 1% to about 20% of fatty component, and
- (c) about 80% to about 99% of a secondary component, as well at its preparation.

## PENETRATION ENHANCEMENT SYSTEMS AND THE PREPARATION THEREOF

The administration of drugs via oral routes is often associated with a variety of problems, eg., first pass metabolism, gastro-intestinal side effects, unpleasant taste and/or odor, and the like.

Recent studies have shown that the transdermal administration of drugs offers a viable alternative to oral dosage forms. However, transdermal delivery systems are not always efficacious due to such factors as the failure of the drug to sufficiently penetrate the cutaneous membrane and enter the body to produce therapeutic systemic effects.

It has been discovered that various drugs can be effectively administered across a body membrane, eg., transdermally, using a novel combination of penetration enhancers.

These enhancers are generally thought of as solvents for the drug or drugs being used, but it is more accurate to term them penetration enhancers since--via a mechanism which is not clearly understood--they assist in the movement of an active ingredient across a living membrane, eg., the skin, and into the body fluid, eg., the blood stream. The systems which enhance transmembranal penetration are generally combinations of fatty acids and/or their esters.

The invention relates to compositions and methods for the administration of bioaffecting agents, eg., drugs, via living membranes, eg., skin, via topical application; ie., by contacting the compositions with the living membranes.

In a preferred embodiment, 0.5-3 wt. % procaterol is combined with 2-90 wt. % linoleic acid and 10-98% propylene glycol to produce compositions useful for transdermal administration.

Other aspects and advantages will be apparent from the following description of the invention.

The compositions and methods of the invention have several advantages over the prior art delivery systems. Since the instant system permits delivery via buccal, rectal, mucosal, nasal and dermal membranes, the drug can enter the bloodstream without entering the gastrointestinal tract. Transmembranal dosage forms generally do not produce the side effects, such as nausea and the like, which are often associated with the oral administration of drugs.

Furthermore, since the instant compositions need not be administered via injection, the unpleasantness of that type of delivery is avoided.

In general, it has been found that administration via penetration of the drug across a suitable membrane, eg., the cutaneous barrier, is superior to other routes of administration, especially in terms of ease of administration and attainment of sustained release.

Weight percentages are based on total composition weight unless staged otherwise.

The bioaffecting agents which can be employed in the compositions of the invention include a wide range of known drug and beneficial substances and/or derivatives thereof.

By "derivatives thereof" is meant pharmaceutically acceptable derivatives of the bioaffecting base, or drug agent, as well as prodrugs and metabolites.

Using procaterol as an illustration, useful derivatives would include procaterol salts, with the hydrochloride salt being exemplary. Other useful forms of procaterol include procaterol base, procaterol sulfate and the like.

Mixtures of one or more such forms of a drug, as well as compositions containing a drug in combination with one or more other drugs, are contemplated.

Depending upon the bioaffecting agent(s) to be employed, a wide range of organic and inorganic salts thereof can be used. The nature of the salt is not essential as long as the drug or other agent maintains its value as a medicament and is compatible with the penetration enhancer(s) or other vehicle(s) employed. Exemplary acid salts include hydrochloride, hydrobromide, orthophosphate, benzoate, maleate, tartarate, succinate, citrate, salicylate, sulfate, acetate, and the like.

Useful bioaffecting agents include:

Antihistamines, such as chlorpheniramine maleate, pheniramine maleate, pyrilamine maleate, doxylamine succinate, and phenyltoloxamine citrate;

Decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, ephedrine;

Various alkaloids, such as codeine phosphate, codeine sulfate and morphine;

Laxatives, vitamins and antacids;

Anticholesterolemic and antilipid agents;

Antiarrhythmics such as N-acetylprocainamide;

Antipyretics and analgesics such as acetaminophen, aspirin, and ibuprofen;  
Appetite suppressants such as phenylpropanolamine hydrochloride or caffeine; and  
Expectorants such as guaifenesin.

6 Additional useful active medicaments include anti-inflammatory substances, coronary dilators, cerebral dilators, vasodilators, anti-infectives, psychotropics, antispasmodics, stimulants, laxatives, decongestants, gastro-intestinal sedatives, antidiarrheal preparations, antitussive drugs, vasodilators, antihypertensive drugs, vasoconstrictors and migraine treatments, antibiotics, tranquilizers, antipsychotics, antitumor drugs, anticoagulants and antithrombotic drugs, hypnotics, sedatives, antiemetics, antinauseants, anticonvulsants, neuromuscular drugs, hyper and hypoglycemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, expectorants, cough suppressants, mucolytics, antidiabetic drugs, and the like. Mixtures may be used.

10 Preferred drugs for use in the instant compositions and methods are: procaterol, 4,5-dihydro-6-[4-(1H-imidazole-1-yl) phenyl]-5-methyl-3-(2H)-pyridazinone morphine, hydromorphone, propranolol, chlorpheniramine and derivatives thereof. Procaterol, the pyridazinone, propranolol and their derivatives are most preferred.

The daily dosages for human use of these preferred drugs are believed to be about 200 mg/day for procaterol and about 2 mg/day. for 4,5-dihydro-6-[4-(1H-imidazole-1-yl) phenyl]-5-methyl-3-(2H)-pyridazinone ("the pyridazinone") and higher for propranolol.

#### Penetration Enhancers

25 The penetration enhancer systems of the invention contain at least one fatty compound in combination with a non-fatty hydroxyl compound.

By "fatty" compounds applicants mean compounds related to, or existing as, any of the saturated or unsaturated monocarboxylic acids that occur naturally in the form of glycerides in fats and fatty oils.

30 The fatty compounds which can be employed are essential fatty acids, their esters, alcohols and other related compounds. Useful fatty components of the instant enhancement systems include saturated and unsaturated aliphatic compounds. Generally the unsaturated compounds contain about 8 to 24 carbon atoms.

Fatty acids, alcohols and esters to be employed herein include those containing oleic, linoleic, linoleic, moieties and the like. Mixtures are contemplated.

35 The preferred group of fatty components include linoleic acid (i.e., 9,12-octadienoic acid) and related compounds. Suitable esters of this or other fatty acid(s) to be employed include the C<sub>1-3</sub> esters e.g., the methyl, ethyl, and propyl esters, and the like.

When an alcoholic fatty component is employed, it is generally preferred that it contain no more than one hydroxyl group, i.e., monohydroxy alcoholic fatty compounds are preferred. One such compound is

40 linoleyl alcohol.

The use of linoleic acid to enhance the penetration of anti-inflammatory and analgesic agents has been described in Kokai Tokyo Kobo. "Topical Anti-inflammatory and Analgesic Agent" Taisho Pharmaceuticals Co., Ltd., Japan, 81, 110, 614 (cl. A61K31/135) September 1, 1981.

In addition, several studies have been made on the function of linoleic acid, an essential fatty acid, in skin. Two of these are: C. Prottey, "Investigation of Functions of Essential Fatty Acids in the Skin," British Journal of Dermatology (1977), 97, 29; and E. O. Butcher, "The Penetration of Fat and Fatty Acid into the Skin of the Rat," J. Invest. Dermatol., 1953, 43-48.

The mechanism by which the linoleic acid or its esters enhances the penetration of the instant combinations is not clearly understood. However, the changes brought about using the instant compositions are systemic and not merely local, i.e., at the site where the composition is applied.

50 The other, or secondary, component of the penetrant system of the invention is not a fatty substance. Generally, this other component is a solvent for the bioaffecting agent. Useful solvents are generally mono- or polyhydroxyl-containing compounds which may, optionally, contain ester groups.

Hydroxyl compounds to be used as the secondary component include compounds containing one or more hydroxyl groups. Polyols are preferred. Polyols containing one to four carbon atoms are more preferred. Propylene glycol, polyethylene glycols (e.g., PEG 400) and tetraglycols are highly preferred. Isopropanol is also useful. Mixtures are operable.

The ester group-containing compound useful in the secondary component of the penetration enhancer system will be at least one compound which contains one or more ester groups. Compounds containing 6 to 30 carbon atoms and three or more ester groups are preferred. Saturated compounds containing about three to about five carbon atoms are more preferred. Triacetin and triethyl citrate are highly preferred. Mixtures are contemplated.

The penetration enhancer systems of the invention contain the primary or fatty component in combination with one or more of the secondary, or non-fatty, components.

Preferred enhancement systems will be composed of a fatty acid or ester, eg., linoleic acid, in combination with a glycol, eg., propylene glycol, and, optionally, an ester, eg., triacetin.

When more than one secondary component is used, the quantities thereof may vary as long as the total quantity of resulting penetrant is beneficial to penetration.

#### The Composition

The compositions which exhibit effective bioavailability when applied transmembranally include the bioaffecting and penetration enhancement portions in the following ranges.

**Table 1**

| <u>Weight Percentage Range</u>    |              |                  |                         |
|-----------------------------------|--------------|------------------|-------------------------|
|                                   | <u>Broad</u> | <u>Preferred</u> | <u>Highly Preferred</u> |
| Bioaffecting agent<br>(eg., drug) | 0.1-10       | 0.2-5            | 2                       |
| Penetration System                | 1-99         | 1-20             | 10                      |
| Fatty Component                   |              |                  |                         |
| Secondary Component               | 0-99         | 80-99            | 90                      |

The following examples illustrate the effectiveness of the penetration enhancers of the invention.

#### Examples

The experimental method employed to generate the data in the following examples was:

Skin sections from male hairless mice (5-7 weeks old) were mounted on Franz® diffusion cells with the stratum corneum facing the donor compartment. To remove extraneous debris, the dermal side of the skin was in contact with saline for 2 hours before starting the diffusion experiment. One milliliter of a procaterol solution was placed in the donor compartment which was then occluded with cellophane and Parafilm®. The appearance of Procaterol in the receiver solution (saline) was monitored by withdrawing the entire contents of the receiver chamber at timed intervals. The receiver compartment was then refilled with fresh saline. The samples were filtered through a 0.45 µ nylon filter and the drug concentration determined by HPLC. Temperature was maintained at 37°C during the experiment.

Procaterol with Linoleic Acid (LA) and Propylene Glycol (PG)

The permeation of procaterol base through hairless mouse skin was significantly enhanced when a penetration system containing propylene glycol was used.

**Table 2**

**Effect of Linoleic Acid Concentration in Propylene Glycol on the Permeation of Procaterol Base**

| Vehicle<br>LA:PG | Drug Conc.<br>ug/mL | Flux<br>ug/cm <sup>2</sup> /h | P<br>cm/sec x 10 <sup>6</sup> | Lag Time<br>(h) |
|------------------|---------------------|-------------------------------|-------------------------------|-----------------|
| 0:100            | 19.1                | 0.45                          | 0.007                         | -               |
| 2:98             | 23.5                | 83.9                          | 0.99                          | 2.7             |
| 5:95             | 21.7                | 125.7                         | 1.6                           | 1.8             |
| 10:90            | 20.71               | 149.7                         | 2.0                           | 1.5             |
| 20:80            | 15.9                | 137.6                         | 2.4                           | 1.1             |
| 50:50            | 21.7                | 159.3                         | 2.04                          | 1.2             |
| 90:10            | 17.05               | 123.4                         | 2.0                           | 1.99            |

Example 2

Procaterol with Linoleic Acid, Triethyl Citrate and Propylene Glycol

Solvent systems containing LA, PG and triethyl citrate (TEC) appear to be highly effective. The flux of procaterol base (PB) from four different formulations (F1 to F4) containing linoleic acid, triethyl citrate, and propylene glycol through hairless mouse skin is shown in Table 4.

**Table 4**

**Permeation of Procaterol from the Formulations Containing Triethyl Citrate**

| Formu-<br>lation | Vehicle<br>LA:TEC:PG   | Drug Conc.<br>mg/mL | Flux<br>ug/cm <sup>2</sup> /h | P<br>cm/sec x 10 <sup>7</sup> | Lag Time<br>(h) |
|------------------|------------------------|---------------------|-------------------------------|-------------------------------|-----------------|
| F1               | 10:80:10               | 16.9                | 32.0                          | 5.26                          | 14.7            |
| F2               | 10:70:20               | 23.03               | 33.5                          | 4.04                          | 14.7            |
| F3               | 20:60:20               | 19.35               | 46.0                          | 6.60                          | 4.9             |
| F4               | 20:50:30               | 44.7                | 65.8                          | 4.10                          | 7.3             |
| F5               | 20:50:30<br>(HCl salt) | 4.32                | 8.5                           | 5.47                          | 11.2            |

The loading capacity of F1 is less than 2%; whereas for F2 to F4 it is more than 2% of PB. The solvent system F5 was saturated with procaterol HCl and the flux of procaterol from this formulation was also measured. The loading capacity of F5 is about 0.5 percent procaterol HCl.

Table 5 shows the total amount of drug that permeated through 10 cm<sup>2</sup> of hairless mouse skin in the first 24 hours of the experiment and the calculated daily flux values (flux mg/cm<sup>2</sup>/h 10 cm<sup>2</sup>24 h). The observed differences between actual and calculated values are due to the lag time.

**Table 5**  
**Total Amount of Procaterol (mg)**  
**Delivered in First 24 Hours of Experiment**

| <u>Formulation</u> | <u>Calculated (mg)</u> | <u>Actual (mg)</u> |
|--------------------|------------------------|--------------------|
| F1                 | 7.68                   | 1.75               |
| F2                 | 8.04                   | 2.9                |
| F3                 | 11.04                  | 9.1                |
| F4                 | 15.79                  | 10.94              |
| F5                 | 2.04                   | 1.1                |

Example 3

Linoleic Acid and Propylene Glycol with 4,5-dihydro-6-[4-(1H-imidazole-1-yl) phenyl]-5-methyl-3-(2H)-pyridazinone.

In this example, the concentration of linoleic acid, a representative fatty acid, in propylene glycol was optimized to achieve a maximum permeability coefficient for the cardiotonic compound 4,5-dihydro-6-[4-(1H-imidazole-1-yl) phenyl]-5-methyl-3-(2H)-pyridazinone.

The base was prepared as follows; One gram of the hydrochloride of the pyridazinone was dissolved in 10 ml of water to which 3 ml of ammonium hydroxide was added. The precipitate (base) thus formed was extracted with chloroform (2 x 15 ml). The chloroform solution was washed with water and dried over anhydrous sodium sulfate. After evaporating the solvent, the pyridazinone base was obtained as a solid powder

The addition of linoleic acid to propylene glycol was found to significantly enhance the permeation of the drug through the skin. A maximum flux was obtained at a linoleic acid concentration of 10%. Table 6 shows the permeability data for the drug, expressed in the terms of the hydrochloride salt.

**Table 6**  
**Effect of Linoleic Acid Concentration**  
**in Propylene Glycol on the Permeation**  
**of Pyridazinone Base (expressed as Cl Salt)**

| <u>% Linoleic Acid</u> | <u>Concentration</u> | <u>Flux (ug/cm<sup>2</sup>)</u> | <u>Permeability Coefficient (P) (cm/sec x 10<sup>7</sup>)</u> | <u>P<sub>x</sub> *</u> | <u>Lag Time (h)</u> |
|------------------------|----------------------|---------------------------------|---------------------------------------------------------------|------------------------|---------------------|
| 0                      | 26.38                | 0.4                             | 0.042                                                         | 1                      | 6.2                 |
| 10                     | 43                   | 492                             | 31.8                                                          | 755                    | 1.75                |
| 40                     | 43                   | 337.3                           | 21.8                                                          | 517                    | 1.45                |
| 80                     | 43                   | 148.5                           | 9.6                                                           | 227                    | 1.29                |
| 100                    | 31.5                 | 24.5                            | 2.2                                                           | 51                     | 5.35                |

\*P<sub>x</sub> = Permeability coefficient of the drug from propylene glycol solution.

Example 4

The results of replacing propylene glycol in the formulations of Example 3 with PEG 400 or with tetraglycol are shown in Table 7.

**Table 7**  
**Effect of Linoleic Acid on Permeation of Drug of**  
**Example 3 in Vehicles Containing PEG 400 or Tetraglycol**

| <u>Vehicle</u> | <u>Concentration</u> | <u>Flux</u><br><u>(<math>\mu\text{g}/\text{cm}^2/\text{h}</math>)</u> | <u>Permeability</u><br><u>Coefficient (P)</u><br><u>(<math>\text{cm}/\text{sec} \times 10^7</math>)</u> | <u>P</u><br><u><math>P_r^*</math></u> | <u>Lag Time</u><br><u>(h)</u> |
|----------------|----------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------|-------------------------------|
| Linoleic acid: |                      |                                                                       |                                                                                                         |                                       |                               |
| PEG 400        | 41.7                 | 114.3                                                                 | 7.6                                                                                                     | 181                                   | 3.5                           |
| 20:80          |                      |                                                                       |                                                                                                         |                                       |                               |
| Linoleic acid: |                      |                                                                       |                                                                                                         |                                       |                               |
| tetraglycol    | 20.09                | 186.69                                                                | 25.8                                                                                                    | 614                                   | 5.58                          |
| 20:80          |                      |                                                                       |                                                                                                         |                                       |                               |

\*Permeability coefficient of the drug from propylene glycol solution

Example 5

**Table 8**

**Effect of Linoleic Acid Concentration  
in Propylene Glycol on the Permeation  
of Propranolol through Hairless Mouse Skin**

| <u>Vehicle</u><br><u>PG:LA</u> | <u>Drug Conc.</u><br><u>(mg/ml)</u> | <u>Flux</u><br><u>(ug/cm<sup>2</sup>/h)</u> | <u>P</u><br><u>(cm/secx10<sup>7</sup>)</u> | <u>Lag Time</u><br><u>(h)</u> |
|--------------------------------|-------------------------------------|---------------------------------------------|--------------------------------------------|-------------------------------|
| 100:0                          | 42                                  | 15.5                                        | 1.03                                       | 3.15                          |
| 98:2                           | 38                                  | 94.3                                        | 6.9                                        | 3.6                           |
| 94:6                           | 52                                  | 60.4                                        | 4.4                                        | 2.8                           |
| 90:10                          | 22                                  | 17.6                                        | 2.2                                        | 1.26                          |
| 60:40                          | 48                                  | 6.2                                         | 0.36                                       | 1.6                           |
| 20:80                          | 57                                  | 4.1                                         | 0.20                                       | 4.6                           |

The maximum permeability coefficient was achieved when the linoleic acid concentration was less than 6%. Table 9 shows the effect of replacing propylene glycol in the formulation with other solvents.

**Table 9**

**Effect of Concentration of Linoleic  
Acid in Various Solvents on the  
Permeation of Propranolol**

| <u>Vehicle</u>    | <u>Drug Conc.</u><br><u>(mg/ml)</u> | <u>Flux</u><br><u>(ug/cm<sup>2</sup>/h)</u> | <u>P</u><br><u>(cm/secx10<sup>7</sup>)</u> | <u>Lag Time</u><br><u>(h)</u> |
|-------------------|-------------------------------------|---------------------------------------------|--------------------------------------------|-------------------------------|
| <u>IP:LA</u>      |                                     |                                             |                                            |                               |
| 98:2              | 77                                  | 88.5                                        | 3.2                                        | 4.4                           |
| 94:6              | 82                                  | 76.6                                        | 2.7                                        | 3.2                           |
| <u>IPM:LA</u>     |                                     |                                             |                                            |                               |
| 60:40             | 50                                  | 4.6                                         | 0.25                                       | 1.98                          |
| <u>PEG 400:LA</u> |                                     |                                             |                                            |                               |
| 20:80             | 51                                  | 3.76                                        | 0.2                                        | 4.6                           |

**Legend**

IP = isopropyl alcohol  
LA = linoleic acid

IPM = isopropyl myristate  
PG = propylene glycol  
PEG = polyethylene glycol

The use of excipients and other conventional additives in the components and methods of the invention are contemplated.

Reasonable variations, such as those which would occur to a skilled artisan, can be made herein without departing from the scope of the invention.



## Claims

1. A transmembranally administrable composition comprising:
  - (a) about 0.2% to about 5% of bioaffecting agent,
  - (b) about 1% to about 20% of fatty component, and
  - (c) about 80% to about 99% of a secondary component.
2. The composition of claim 1 wherein the bioaffecting agent is a drug.
3. The composition of Claim 2 wherein the fatty component is selected from the group consisting of linoleic acid, linoleic esters, and linoleyl alcohols.
4. The composition of Claim 3 wherein the secondary component contains a hydroxyl-containing compound.
5. The composition of Claim 3 wherein the secondary component contains at least one compound selected from the group consisting of isopropanol, propylene glycol, polyethylene glycol 400 and tetraglycol.
6. The composition of Claim 4 further comprising an ester compound.
7. The composition of claim 6 wherein the ester compound is at least one compound selected from the group consisting of triacetin and triethyl citrate.
8. Use of a transmembranally administrable composition according to Claims 1 to 7 for the manufacture of pharmaceutical preparations useful in the treatment of a living membrane.

### Claims for the following Contracting States: AT; ES; GR

1. Process for the manufacture of a transmembranally administrable pharmaceutical preparation comprising the incorporation of
  - (a) about 0.2% to about 5% of bioaffecting agent,
  - (b) about 1% to about 20% of fatty component, and
  - (c) about 80% to about 99% of a secondary component.
2. Process of Claim 1 wherein the bioaffecting agent is a drug.
3. Process of Claim 2 wherein the fatty component is selected from the group consisting of linoleic acid, linoleic esters, and linoleyl alcohols.
4. Process of Claim 3 wherein the secondary component contains a hydroxyl-containing compound.
5. Process of Claim 3 wherein the secondary component contains at least one compound selected from the group consisting of isopropanol, propylene glycol, polyethylene glycol 400 and tetraglycol.
6. Process of Claim 4 further comprising the addition of an ester compound.
7. Process of Claim 6 wherein the ester compound is at least one compound selected from the group consisting of triacetin and triethyl citrate.
8. Use of a transmembranally administrable composition according to Claims 1 to 7 for the manufacture of pharmaceutical preparations useful in the treatment of a living membrane.



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# EUROPEAN SEARCH REPORT

Application Number

EP 87 11 2412

| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                     |                                                                               |                                                                                                                                                                                                                                                                              |                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Category                                                                                                                                                                                                                | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim                                                                                                                                                                                                                                                            | CLASSIFICATION OF THE APPLICATION (Int. Cl.4) |
| X                                                                                                                                                                                                                       | EP-A-0 129 283 (PROCTER & GAMBLE)<br>* example 6 *<br>---                     | 1-6, 8                                                                                                                                                                                                                                                                       | A 61 K 47/00                                  |
| Y                                                                                                                                                                                                                       | EP-A-0 095 813 (PROCTER & GAMBLE)<br>* claims 1, 4 *<br>---                   | 1-8                                                                                                                                                                                                                                                                          |                                               |
| Y                                                                                                                                                                                                                       | EP-A-0 043 738 (PROCTER & GAMBLE)<br>* page 28, lines 5-8 *<br>---            | 1-8                                                                                                                                                                                                                                                                          |                                               |
| Y                                                                                                                                                                                                                       | EP-A-0 144 069<br>(MAX-PLANCK-GESELLSCHAFT)<br>* claim 1 *<br>-----           | 7                                                                                                                                                                                                                                                                            |                                               |
|                                                                                                                                                                                                                         |                                                                               |                                                                                                                                                                                                                                                                              | TECHNICAL FIELDS SEARCHED (Int. Cl.4)         |
|                                                                                                                                                                                                                         |                                                                               |                                                                                                                                                                                                                                                                              | A 61 K 47/00                                  |
| The present search report has been drawn up for all claims                                                                                                                                                              |                                                                               |                                                                                                                                                                                                                                                                              |                                               |
| Place of search<br>BERLIN                                                                                                                                                                                               |                                                                               | Date of completion of the search<br>26-11-1987                                                                                                                                                                                                                               | Examiner<br>NATUS                             |
| CATEGORY OF CITED DOCUMENTS                                                                                                                                                                                             |                                                                               |                                                                                                                                                                                                                                                                              |                                               |
| X : particularly relevant if taken alone<br>Y : particularly relevant if combined with another document of the same category<br>A : technological background<br>O : non-written disclosure<br>P : intermediate document |                                                                               | T : theory or principle underlying the invention<br>E : earlier patent document, but published on, or after the filing date<br>D : document cited in the application<br>L : document cited for other reasons<br>& : member of the same patent family, corresponding document |                                               |